WHAT IS BEHIND ISCHEMIC NEURONAL DAMAGEA ? HOW DOES MILD HYPOTHERMIA MODULATE IT ?

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The mechanisms of ischemic neuronal damage should be clarified fully in order to find out essential measures against stroke, transient cardiac arrest or head injury. A growing body of evidence indicates that excitotoxicity may play an important role in the ischemic damage; briefly, a sharp and a large scale extracellular elevation of glutamate, followed by intracellular mobilization of calcium, which eventually damage mitochondrial respiration or destroy cytoskeletons. Our studies on ischemia-induced cellular events in pyramidal neurons of hippocampal CA1 of the gerbil revealed that, within 10sec after ischemic insult, spontaneous firings totally disappear. The extracellular glutamate elevation starts in following 20-30 sec reaching the level 20 folds the preischemic one at 5 min of ischemia. Calcium mobilization, both inflow and discharge from inner stores, occur after 150-180sec latency following a simultaneous membrane depolarization and a striking drop of energy charge. After reperfusion at this time point these apparently recovered. However, the pyramidal neurons almost totally die after 70-80 hrs exclusively in CA1, leaving CA3 or dentate gyrus undamaged, which is now widely known as the delayed neuronal death. This type of death, which may happen in penumbra region of stroke or in the transient cardiac arrest, has chances to be resuscitated by medical treatments even some hrs after attack.

Protection against such ischemic processes has been attempted; for instance, inhibitors of glutamate release, antagonists of glutamate receptors, inhibitors of calcium mobilization, scavengers to superoxides, endogenous modulators like adenosine etc. However, none of them is yet satisfactorily introduced in clinical field. On the other hand, mild hypothermia reduces the glutamate elevation and the calcium mobilization and depress a long-lasting activation of glutamate receptors; and not only in animal experiments but also in clinical trials, marked beneficial effects were recently obtained. In this communication these recent results will be summarized.